MicroRNAs control hepatocyte proliferation during liver regeneration.

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Public Summary:
The study shows that of all mouse microRNAs, microRNA-21 (miR-21) is most significantly induced during liver regeneration. Furthermore, the findings suggest that miR-21 is needed for entry of regenerating hepatocytes into S phase, which raises the possibility that miR-21 could be targeted for therapy of liver failure.

Scientific Abstract:
MicroRNAs (miRNAs) constitute a new class of regulators of gene expression. Among other actions, miRNAs have been shown to control cell proliferation in development and cancer. However, whether miRNAs regulate hepatocyte proliferation during liver regeneration is unknown. We addressed this question by performing 2/3 partial hepatectomy (2/3 PH) on mice with hepatocyte-specific inactivation of DiGeorge syndrome critical region gene 8 (DGCR8), an essential component of the miRNA processing pathway. Hepatocytes of these mice were miRNA-deficient and exhibited a delay in cell cycle progression involving the G(1) to S phase transition. Examination of livers of wildtype mice after 2/3 PH revealed differential expression of a subset of miRNAs, notably an induction of miR-21 and repression of miR-378. We further discovered that miR-21 directly inhibits Btg2, a cell cycle inhibitor that prevents activation of forkhead box M1 (FoxM1), which is essential for DNA synthesis in hepatocytes after 2/3 PH. In addition, we found that miR-378 directly inhibits ornithine decarboxylase (Odc1), which is known to promote DNA synthesis in hepatocytes after 2/3 PH. CONCLUSION: Our results show that miRNAs are critical regulators of hepatocyte proliferation during liver regeneration. Because these miRNAs and target gene interactions are conserved, our findings may also be relevant to human liver regeneration.